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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/405,454	03/15/95	SULLIVAN J	4249.0002-05

SCHWADRON, EXAMINER

18N1/0801

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ART UNIT	PAPER NUMBER
1816	21

DATE MAILED: 08/01/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 4/30/96 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 40-49 are pending in the application.

Of the above, claims _____ are withdrawn from consideration.

2. ☒ Claims 1-34 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 40-49 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

15. Claims 40-49 are under consideration. Claims 27,29, 37-39 have been cancelled.

RESPONSE TO APPLICANT'S ARGUMENTS

16. Applicants need to update the status of all US patent applications (eg. abandoned, etc.) disclosed in the specification (eg. 08/277,288 on page 1).

17. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

18. Claims 40-49 stand rejected under 35 U.S.C. § 103 as being unpatentable over Sullivan et al. in view of Coulter et al. and Smith et al. as evidenced by Stedman's Medical Dictionary (1977).

The claims are drawn to antivenin compositions consisting of F(ab) fragments. Sullivan et al. teach purified antivenin polyvalent antibodies derived from horse hyperimmune antisera against venom of the Crotalus genus (see *Methods* section, pages 185-187). These antibodies are predominantly IgG(T), because that is the predominant isotype found in hyperimmune horse antisera. A routineer would have immunized horses to produce said hyperimmune antisera because this is the art recognized procedure for producing antivenin. Sullivan et al. do not teach a F(ab) containing antivenin.

Coulter et al. teaches a method for producing F(ab) fragments that are free of Fc (see abstract). Coulter et al. teaches a composition of F(ab) fragments of antibody against textilotoxin (a snake toxin) (see pages 201-203). Stedman's Medical Dictionary defines antivenin as "an antitoxin specific for an animal or insect toxin"(page 94). Therefore the composition taught by Coulter et al. is an antivenin. The F(ab) composition (page 201, third paragraph) was derived from polyclonal antisera against textilotoxin (page 199, second paragraph). The F(ab) produced by said method were free of Fc and extraneous protein (see Abstract). A routineer would have assayed for Fc by immunoelectrophoresis using anti-Fc antibodies or any other art recognized procedure.

Smith et al. teaches the advantages of F(ab) fragments for the neutralization and clearance of toxic substances in therapeutic applications (see page 393, first paragraph, *Discussion* section). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have produced antivenin compositions consisting of F(ab) fragments because Sullivan et al. teach purified antivenin polyvalent antibodies

derived from horse hyperimmune antisera against venom of the Crotalus genus, a routineer would have used the procedure of Sullivan et al. to produce purified antivenin antibodies against any desired venom, Coulter et al. teaches a method for producing antivenin F(ab) fragments that are free of Fc, and Smith et al. teaches the advantages of F(ab) fragments for the neutralization and clearance of toxic substances in therapeutic applications. One of ordinary skill in the art would have been motivated to do the aforementioned because Smith et al. teaches that,

"Relatively rapid clearance of Fab fragments can be used to advantage when the objective is rapid neutralization and clearance of a toxic substance, and purified sheep digoxin specific Fab fragments have been utilized clinically for the reversal of advanced digoxin intoxication. This therapeutic approach is based on similar binding properties and the postulated lesser immunogenicity of Fab compared with IgG. For urgent clinical situations such as life threatening digitalis-toxic cardiac arrhythmias, the present study indicates that Fab has another important advantage-more rapid and extensive distribution to its presumed site of action in the interstitial space." (page 393). Further motivation is provided by the teaching of Coulter et al. that F(ab) antivenin can be made and that said antivenin work in vivo to neutralize snake toxins (see page 202, third paragraph). In addition, Sullivan et al. teach that reducing the immunogenicity of polyvalent horse antivenin is an important goal, due to immune reactions that limit the clinical efficacy of antivenin preparations which contain only partially purified hyperimmune horse antisera (see page 185, first paragraph).

Applicants arguments in the amendment filed 4/30/96 have been considered and deemed not persuasive. Regarding applicants comments on pages 6-8 of the instant amendment, Coulter et al. teach that F(ab) antivenin can be made and that said antivenin work in vivo to

neutralize snake toxins (see page 202, third paragraph). Thus, the Smith et al. reference is relied on only to teach the advantages of using F(ab) in vivo, while Coulter et al. have already shown that F(ab) antivenin work in vivo to neutralize snake toxins. Smith et al. teach that F(ab) are less immunogenic than the antibody from which they are derived (see page 395). Smith et al. teaches that,

"Relatively rapid clearance of Fab fragments can be used to advantage when the objective is rapid neutralization and clearance of a toxic substance, and purified sheep digoxin specific Fab fragments have been utilized clinically for the reversal of advanced digoxin intoxication. This therapeutic approach is based on similar binding properties and the postulated lesser immunogenicity of Fab compared with IgG." (page 393). Thus, Smith et al. establishes the advantages of using F(ab) antivenin, while Coulter et al. establishes that said antivenin can neutralize snake venom toxin in vivo. Regarding applicants comments on page 8 of the instant amendment, Coulter et al. establishes that F(ab) antivenin can neutralize snake venom toxin in vivo. Regarding the Faulstich et al. reference said reference teaches that monoclonal antibody against α amatoxin cannot be used to treat α amatoxin and that F(ab) obtained from said antibody also cannot be used to treat α amatoxin. Thus, the circumstances surrounding treatment of α amatoxin poisoning differ from treatment of snake venom because the use of antibody to treat snake venom is well known in the art and Coulter et al. teach that F(ab) antivenin can be made and that said antivenin work in vivo to neutralize snake toxins (see page 202, third paragraph). Regarding applicants comments on page 9 of the instant amendment about Balthasar et al., Balthasar et al. refer to α amatoxin, which is a toxin which cannot be treated with antibodies as shown by Faulstich et al. The circumstances surrounding treatment of α amatoxin poisoning differ from treatment of snake venom because the use of antibody to treat snake venom is

well known in the art and Coulter et al. teach that F(ab) antivenin can be made and that said antivenin work in vivo to neutralize snake toxins (see page 202, third paragraph). Furthermore, Balthasar et al. teach that the use of drug-binding antibodies and antibody fragments for the treatment of drug intoxication is well known. (see Abstract, last sentence). Thus, there are no negative teachings in Faulstich et al. or Balthasar et al. that would suggest that F(ab) antivenin could not be used to treat snake venom poisoning.

Regarding applicants comments on page 10 of the instant amendment, it would have been obvious to a routineer that since antivenin antibody against Crotalus venom was known in the art, and Coulter et al. establish that F(ab) antivenin can be used to treat snake venom, that F(ab) antivenin against Crotalus venom could have been used to treat Crotalus venom. The antibody antivenin against Crotalus venom from which F(ab) would have been prepared was already known in the art and consisted of antibodies against toxins occurring in Crotalus venom. Regarding applicants comments on page 11, the efficacy of antibody against Crotalus venom was already known in the art. There is no evidence of record that suggests that it would have been unpredictable that F(ab) derived from said antibody could have been used as antivenin. Coulter et al. have already established that F(ab) antivenin can be used to treat snake venom. Regarding applicants comments on page 11, second paragraph, Coulter et al. establish that F(ab) antivenin can be used to neutralize snake toxin. Smith et al. teaches that F(ab) has a greater biodistribution in vivo than IgG from which the F(ab) were derived (see page 384, first paragraph). The greater volume of biodistribution of F(ab) results from the smaller size of F(ab) in distinction to the intact antibody. Thus, Coulter et al. teaches that F(ab) antivenin can neutralize snake venom toxin and Smith et al. teaches that F(ab) have greater biodistribution such that the

F(ab) would be more likely that intact antibody to distribute to the proper anatomical location to encounter snake venom that was administered. Thus, there is no reason to doubt that F(ab) could be used to treat snake venom poisoning. The F(ab) antivenin against Crotalus venom would have been derived from art known antibody against Crotalus venom which is polyclonal and contains antibodies against various toxins found in Crotalus venom.

Regarding the Smith declaration and Sullivan declaration, both declarations ignore the fact that Coulter et al. teaches that F(ab) antivenin can neutralize snake venom toxin. Furthermore, regarding the use of F(ab) antivenin, Sullivan (1986) teaches that:

"Recently, investigations have resulted in the production of active Fab and Fab2 fragments from the IgG(T)(Sullivan et al. 1984). Studies with these fragments are ongoing and may be a promising new immunotherapeutic agent for human envenomations."(page 56, first column).

Sullivan (1986) also teaches that:

"Since Fab fragments have the same affinity for antigen as IgG, they are better suited for toxin and drug neutralization as well as for enhancing their elimination." (page 50, column 1).

Thus, Sullivan (1986) establishes that the art recognized that there would have been a reasonable expectation of success that the claimed invention would have worked.

Regarding applicants comments about longfelt need on page 13 of the instant amendment, there is no evidence submitted that the FDA recognized a need for improved antivenin or that the FDA recognized that the claimed invention was an improved antivenin. Furthermore, Sullivan (1986) establishes that F(ab) antivenin was known in the art as of 1986. The antibody preparation that is disclosed in the FDA documents is an ovine preparation which is not disclosed in the instant application, which only discloses horse derived antibody preparations. With regards to the clinical study

depicted in paragraphs 12 and 13 of the Smith declaration, there is no disclosure in the specification of TAb001, or a F(ab) fragment containing antisera against Vipera berus. None of the claims under consideration read on antivenin against Vipera berus.

OTHER REJECTIONS

19. The following new grounds of rejection were necessitated by applicants amendment.

20. Claims 43,44,48,49 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 43 is substantially duplicative of claim of claim 41, because both claims read on the same product. Claim 44 is substantially duplicative of claim of claim 42, because both claims read on the same product. Claim 48 is substantially duplicative of claim of claim 46, because both claims read on the same product. Claim 49 is substantially duplicative of claim of claim 49, because both claims read on the same product.

21. Claims 45-49 are rejected under 35 U.S.C. § 103 as being unpatentable over Sullivan et al. in view of Coulter et al.

The claims are drawn to F(ab) fragments. Sullivan et al. teach purified antivenin polyvalent antibodies derived from horse

hyperimmune antisera against venom of the Crotalus genus (see *Methods* section, pages 185-187). These antibodies are predominantly IgG(T), because that is the predominant isotype found in hyperimmune horse antisera. A routineer would have immunized horses to produce said hyperimmune antisera because this is the art recognized procedure for producing antivenin. Sullivan et al. do not teach a F(ab) against Crotalus venom.

Coulter et al. teaches a method for producing F(ab) fragments that are free of Fc (see abstract). Coulter et al. teaches a composition of F(ab) fragments of antibody against textilotoxin (a snake toxin) (see pages 201-203). The F(ab) composition (page 201, third paragraph) was derived from polyclonal antisera against textilotoxin (page 199, second paragraph). The F(ab) produced by said method were free of Fc and extraneous protein (see Abstract). A routineer would have assayed for Fc by immunoelectrophoresis using anti-Fc antibodies or any other art recognized procedure. Coulter et al. teach that: "Fab fragments of IgG have been used in enzyme immunoassay instead of IgG (Kato et al. 1976). EIAs of higher sensitivity have been claimed when Fab enzyme is used instead of IgG enzyme." (page 199, first paragraph).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have produced the claimed F(ab) fragments because Coulter et al. teaches that: "EIAs of higher sensitivity have been claimed when Fab enzyme is used instead of IgG enzyme" and therefore a routineer would have produced the F(ab) against Crotalus venom for use in EIAs to detect said venom.

22. Papers related to this application may be submitted to Group 180 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG

30 (November 15, 1989). Papers should be faxed to Group 180 at (703) 305-7401.

23. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Dr. Ron Schwadron whose telephone number is (703) 308-4680. The examiner can normally be reached Tuesday through Friday from 8:30 to 6:00. The examiner can also be reached on alternative Mondays. A message may be left on the examiners voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ms Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.

RONALD B. SCHWADRON
PRIMARY EXAMINER
GROUP 1800

Ron Schwadron, Ph.D.
Primary Examiner
Art Unit 1816
July 31, 1996